New Predictors in Determining the Need for Invasive Treatment in NSTEMI During the COVID-19 Pandemic? A Retrospective Study

Ekrem Aksu[1], Deniz Avcı[2], Enes Çelik[1], Bayram Öztürk[1], Mehmet Buğra Bozan[3], Kemal Göçer[4], Ahmet Çağrı Aykan[1]

[1] Department of Cardiology, Faculty of Medicine, University of Kahramanmaras Sutcu Imam, Kahramanmaras, Turkey

[2] Department of Internal Medicine, Kayseri Training and Research Hospital, Kayseri, Turkey

[3] Department of General Surgery, Faculty of Medicine, University of Kahramanmaras Sutcu Imam, Kahramanmaras, Turkey

[4] Department of Cardiology, Necip Fazıl City Hospital, Kahramanmaras, Turkey

ABSTRACT

Introduction: The non-invasive approach has become the first choice for the acute non-ST elevation myocardial infarction-acute coronary syndrome (NSTEMI-ACS) during the Coronavirus Disease-2019 (COVID-19) pandemic. However, most of these patients require interventional treatment. In this study, the possible role of hematological inflammatory markers in differentiating medium-high risk NSTEMI-ACS patients according to the GRACE risk classification in need of interventional treatment was investigated.

Patients and Methods: Patients who underwent coronary angiography with the diagnosis of NSTEMI-ACS in a tertiary cardiology clinic between January 2018 and December 2019 were included in the study, which was designed as a retrospective cohort study. NSTEMI-ACS patients (n= 276), except for patients with exclusion criteria (n= 32), were divided into two groups as those in need of invasive treatment (n= 217) and medical treatment (n= 59) according to the results of coronary angiography. The hematological inflammatory markers were compared between groups.

Results: Neutrophil to lymphocyte ratio (NLR) (AUC: 0.637, 95% CI: 0.563-0.712, p= 0.001) and systemic immune-inflammation index (SII) (AUC: 0.622, 95% CI: 0.545-0.699, p= 0.004) predicted the requirement of interventional treatment in NSTEMI-ACS.

Conclusion: It is unclear whether the NLR and SII elevation, which may be a predictor of the need for invasive treatment, is a cause or a consequence of the pathophysiological process in patients with NSTEMI-ACS. However, elevated NLR and SII values can help distinguish NSTEMI-ACS patients who need invasive treatment during the COVID-19 pandemic. The results of this study, show the need for large-sized studies to determine the ideal cut-off point of NLR and SII levels in determining the treatment strategy for NSTEMI-ACS.

Key Words: Non-ST elevation myocardial infarction; invasive treatment; neutrophil to lymphocyte ratio; systemic immune-inflammation index.

COVID-19 Pandemisi Sırasında NSTEMI Hastalarında İnvaziv Tedavi İhtiyacını Belirlemede Yeni Öngörücüler? Geriye Dönük Bir Çalışma

ÖZ

Giriş: Noninvaziv yaklaşım, "Coronavirus Disease-2019 (COVID-19)" pandemisi sırasında akut ST yükselmesiz miyokart infarktüsü-akut koroner sendrom (NSTEMI-AKS) için ilk seçenek haline gelmiştir. Ancak bu hastaların çoğu girişimsel tedaviye ihtiyaç duyar. Bu çalışmada, girişimsel tedaviye ihtiyaç duyan GRACE risk sınıflandırmasına göre orta-yüksek riskli NSTEMI-AKS hastalarını ayırt etmede hematolojik inflamatuvar belirteçlerin olası rolü araştırılmıştır.

Hastalar ve Yöntem: Geriye dönük kohort çalışması olarak tasarlanan çalışmaya Ocak 2018-Aralık 2019 tarihleri arasında üçüncü basamak kardiyoloji kliniğinde NSTEMI-AKS tanısı ile koroner anjiyografi yapılan hastalar dahil edilmiştir. AKS hastaları (n= 276), dışlama kriterleri olan hastalar (n= 32) dışındaki sonuçlara göre invaziv tedavi (n= 217) ve medikal tedavi (n= 59) olmak üzere iki gruba ayrılmıştır. Hematolojik inflamatuvar belirteçler gruplar arasında karşılaştırılmıştır.

Bulgular: Nötrofil lenfosit oranı (NLR) (EAA: 0.637, %95 CI: 0.563-0.712, p= 0.001) ve sistemik immün inflamasyon indeksi (SII) (EAA: 0.622, %95 CI: 0.545-0.699, p= 0.004) NSTEMI-AKS'de girişimsel tedavi gerekliliğini öngörmüştür.

Sonuç: İnvaziv tedavi ihtiyacının bir göstergesi olabilecek NLR ve SII yükselmesinin, NSTEMI-AKS'li hastalarda patofizyolojik sürecin bir nedeni mi yoksa bir sonucu mu olduğu açık değildir. Bununla birlikte,

Cite this article as: *Aksu E, Avcı D, Çelik E, Öztürk B, Bozan MB, Göçer K, et al. New predictors in determining the need for invasive treatment in NSTEMI during the COVID-19 pandemic? A retrospective study. Koşuyolu Heart J 2021;24(1):1-7.*

Correspondence

Ekrem Aksu

E-mail: drekremaksu4676@gmail.com

Submitted: 26.02.2021
Accepted: 02.03.2021
Available Online Date: 01.04.2021

yüksek NLR ve SII değerleri, COVID-19 pandemisi sırasında invaziv tedaviye ihtiyaç duyan NSTEMI-AKS hastalarını ayırt etmeye yardımcı olabilir. Bu çalışmanın sonuçları, NSTEMI-AKS için tedavi stratejisini belirlemede NLR ve SII seviyelerinin ideal kesme noktasını belirlemek için büyük ölçekli çalışmalara olan ihtiyacı göstermektedir.

Anahtar Kelimeler: ST yükselmesiz miyokart infarktüsü; invaziv tedavi; nötrofil lenfosit oranı; sistemik immün inflamasyon indeksi.

INTRODUCTION

Non-ST elevation myocardial infarction-acute coronary syndrome (NSTEMI-ACS) is one of the cardiac emergencies where early diagnosis and treatment are important. In the guidelines, diagnostic coronary angiography is recommended within 24 hours at the latest in patients with NSTEMI-ACS[1]. However, in the national consensus statement published in the period of Coronavirus Disease-2019 (COVID-19), non-invasive treatment was recommended as an alternative therapy in patients with non-very high risk NSTEMI-ACS[2,3]. Unfortunately, risk scoring systems are not sufficient to differentiate these patients. Therefore, it is important to discover markers that can be used to differentiate NSTEMI-ACS patients with increased invasive treatment during the COVID-19 pandemic.

Inflammation plays an active role in the development and progression of atherosclerotic plaque in the coronary artery. It has been reported that coronary artery patients with severe atherosclerotic involvement and high mortality rates may be distinguished with the help of hematological markers closely related to inflammation[4,5]. To the best of our knowledge, there is a lack of literature on the correlation between the need for invasive treatment strategy and the hematological markers in patients diagnosed with NSTEMI-ACS.

In this study, the potential role of hematologic inflammatory markers in differentiating those requiring invasive treatment in patients with medium-high risk NSTEMI-ACS according to the Global Registry of Acute Coronary Events (GRACE) risk classification was investigated[6].

PATIENTS and METHODS

The study was designed as a retrospective cohort study. Study data were obtained from medical records. Between January 2018 and December 2019, patients treated with a diagnosis of NSTEMI-ACS in the cardiology clinic of a tertiary hospital were consecutively evaluated. NSTEMI-ACS was defined as ischemic chest pain with troponin-I levels > 0.01 ng/mL and non-ST segment elevation on 12-lead chest electrocardiography (ECG).

Inclusion criterias: Patients who do not have exclusion criteria and who underwent coronary angiography with the diagnosis of NSTEMI-ACS.

Exclusion criterias: Being under the age of 18, chest pain that persists despite medication, hemodynamic instability, fatal ventricular arrhythmias, and the presence of dynamic ST-T wave changes, heart failure (ejection fraction < 40), severe anemia, malignancy, sepsis, obesity [body mass index (BMI) > 30 kg/m^2], renal failure (glomerular filtration rate < 60 mL/min/1.73 m^2), chronic hematological disease, collagen tissue disease, moderate to severe hepatic failure, severe valvular heart disease, electrolyte disturbance, chronic anti-inflammatory drug use, history of chronic inflammatory disease, and a history of serious infection in the last month.

NSTEMI-ACS patients (n= 276), except for patients with exclusion criteria (n= 32), were divided into two groups as those in need of invasive treatment (n= 217) and medical treatment (n= 59) according to the results of coronary angiography (Figure 1).

BMI was calculated by dividing the weight in kilograms by the square of height in meters. GRACE risk scores for each patient at admission were calculated with the help of a computer program (http://www.outcomes-umassmed.org/grace). We admitted to the Clinicaltrials.gov with the aprotocol number 05.08.2020-2020/15/10 and we are waiting for approval.

Complete blood count parameters obtained from the blood taken during hospitalization using an automatic hematological analyzer (XN 3000; Sysmex Corp., Kobe, Japan) were obtained from the records. Among these parameters, hemoglobin, hematocrit, red cell distribution width (RDW), mean platelet volume (MPV), platelet distribution width (PDW), thrombocyte (P), white blood cells (WBC), immature granulocyte count (IGC), lymphocyte (L) and neutrophil (N) counts was recorded. The N/L ratio (NLR) was determined by dividing the N number by the L number. The P/L ratio (PLR) was determined by dividing the P number by the L number. Systemic Immune-inflammation Index (SII) was calculated using P x NLR formula[7]. Routine biochemical tests of each patient, were carried out the next morning after hospitalization, after 12 hours of fasting.

Two interventional cardiologists blinded to the study made angiographic assessments and calculated the Gensini score of each patient[8]. TIMI 0-1 flow in the coronary arteries on angiography was defined as complete occlusion.

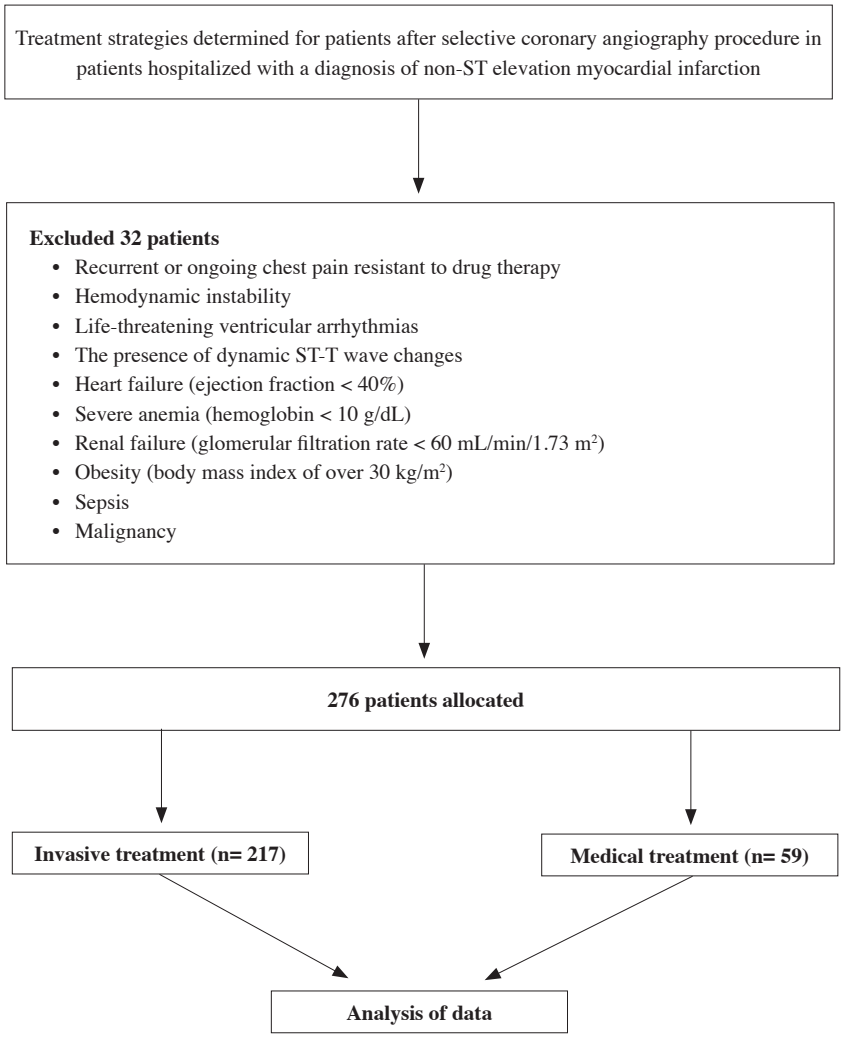

Figure 1. The enrollment of the study population was shown in flow chart.

All echocardiographic assessments were made in line with the recommendations of the guidelines by the American Heart Association[9].

Whether the continuous variables fit the normal distribution was evaluated using the Shapiro-Wilk test and histograms. Continuous variables were presented as mean and standard deviation, and as median (25^{th} percentile-75^{th} percentile) if they were not normally distributed. In the comparison between groups, Student's t-test was used in accordance with normal distribution, if not, the Mann-Whitney U test was used. Chi-square test or Fisher's exact test was used to compare categorical variables. The power of the parameters to predict the type of treatment or total occlusion was measured by receiver operating characteristic curves (ROC) calculations. The statistical significance limit was chosen as $p< 0.05$. All statistical calculations were carried out using SPSS v.23.

RESULTS

Participants were divided into two groups as an invasive treatment and medical treatment. Demographic data, comorbidities and the drugs they used were similar between the groups (Table 1).

The main concern in the study was the comparisons of markers that indicate inflammation between the two groups. There was a significant difference between the two groups in terms of WBC ($p< 0.001$), SII ($p= 0.004$), and NLR ($p= 0.004$) (Table 1). Multivariate analyses and ROC analyzes were performed to evaluate the predictive power of these parameters for invasive treatment. WBC, NLR, and SII were found to predict moderately invasive treatment in patients. It was observed that IGC values, which were found to be significantly higher in multivariate analysis, did not have predictive value in ROC analysis (Figure 2, Table 2, 3).

Table 1. Demographic and laboratory findings of patients in need of invasive and medical treatment strategies

	Treatment groups		
	Invasive treatment (n= 217)	**Medical treatment (n= 59)**	**p value**
Age (years) [mean ± SD (min-max)]	67.00 ± 12.56 (59-76)	68.44 ± 15.27 (60-80)	0.509[A]
Male/Female (gender)	69.6%/30.4% (n= 151/66)	54.2%/45.8% (n= 32/27)	***0.027***[C]
BMI (kg/m^2) [median (25%-75%)]	27.36 (26.5-28.2)	27.27 (26.8-28)	0.504[B]
Systolic TA (mmHg) [median (25%-75%)]	130 (125-135)	130 (125-135)	0.918[B]
Diastolic TA (mmHg) [median (25%-75%)]	72 (70-76)	74 (72-76)	0.184[B]
Hypertension	67.3% (n= 146/217)	64.4% (n= 38/59)	0.678[C]
Dyslipidemia	29.0% (n= 63/217)	27.1% (n= 16/59)	0.773[C]
DM	32.3% (n=70/217)	33.9% (n=20/59)	0.812[C]
GRACE score	120 (110-135)	122 (115-125)	0.385[B]
Gensini score	32 (16-44)	8 (4-12)	***< 0.001***[B]
ACE/ARBs	52.1% (n= 113/217)	59.3% (n= 35/217)	0.322[C]
Beta-blockers	43.8% (n= 95/217)	37.3% (n= 22/217)	0.371[C]
HCT [median (25%-75%)]	40.7% (36.8-43.9)	38.1% (35.45-42.65)	0.11[B]
CCB	25.3% (n= 55/217)	23.7% (n= 14/59)	0.799[C]
Statins	28.6% (n= 62/217)	27.1% (n= 16/59)	0.826[C]
OAD	30.4% (n= 66/217)	27.1% (n= 16/59)	0.623[C]
Insulin usage	12.9% (n= 28/217)	11.9% (n= 7/59)	0.832[C]
EF [median (25%-75%)]	55% (50-60)	55% (55-55)	0.591[B]
WBC (10^3/mm^3) [median (25%-75%)]	9.84 (8.33-11.79)	8.58 (7.17-10.21)	***< 0.001***[B]
IGC (/mm^3) [median (25%-75%)]	40 (20-55)	40 (20-60)	***0.648***[B]
RDW-CV [median (25%-75%)]	13.5% (12.9-14.8)	14 (13.25-14.9)	0.128[B]
MPV (fL) [median (25%-75%)]	10.4 (9.7-11.1)	10.2 (9.8-10.85)	0.247[B]
PDW [median (25%-75%)]	12.3% (11-13.6)	12.2 (11.2-13.75)	0.914[B]
SII [median (25%-75%)]	945.93 (602.15-1518.79)	738.79 (450.55-1085.98)	***0.004***[B]
NLR [median (25%-75%)]	3.71 (2.47-6.42)	2.72 (2.09-3.91)	***0.001***[B]
PLR [median (25%-75%)]	129.56 (96.36-187.24)	126.74 (19.44-552.02)	0.858[B]

A: p< 0.05 according to Student t-test.
B: p< 0.05 according to Mann-Whitney U test.
C: p< 0.05 according to Chi-square test.

TA: Blood pressure arterial, BMI: Body mass index, ACE/ARBs: Angiotensin converting enzyme inhibitors/Angiotensin receptor blockers, HCT: Hydrochlorotiazid, CCB: Calcium channel blockers, OAD: Oral antidiabetics, EF: Ejection fraction, WBC: White blood cell count, IGC: Immature granulocyte count, RDW: Relation of red cell distribution width, MPV: Mean platelet volume, PDW: Platelet distribution width, SII: Systemic immune-inflammation index, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio.

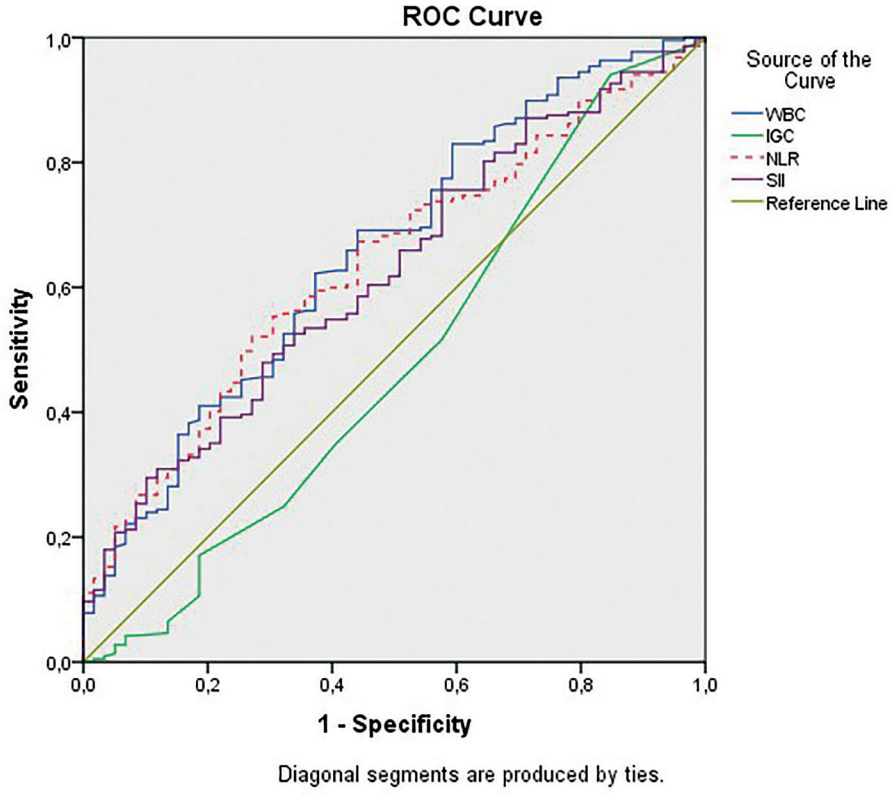

Figure 2. The relationship of WBC, IGC, NLR, and SII levels with the need for invasive treatment in NSTEMI-ACS.

Table 2. Multivariate analyses results of inflammatory markers for prediction of patients in need of invasive treatment strategies

				95% CI	
	Odds Ratio	B value	p value	Lower Bound	Upper Bound
WBC	0.915	10.373	***< 0.001****	9.996	10.749
NLR	0.351	5.792	***< 0.001****	4.855	6.729
IGC	0.986	10.471	***< 0.001****	10.321	10.620
SII	0.359	1426.354	***< 0.001****	1199.723	1652.986

WBC: White blood cell count, NLR: Neutrophil to lymphocyte ratio, IGC: Immature granulocyte count, SII: Systemic immune-inflammation index, CI: Coefficient Interval.
* The difference is statistically significant.

Table 3. ROC analyzes results of inflammatory markers for prediction of patients in need of invasive strategies

					Asymptotic 95% CI		
	ARUC	Cut-off value	Sensitivity (%)	Specificity (%)	Lower Bound	Upper Bound	p value
WBC (10^3/mm^3)	0.657	≥ 9	69.1	52.5	0.578	0.735	***< 0.001****
NLR	0.637	≥ 2.81	66.8	55.9	0.563	0.712	***0.001****
IGC (/mm^3)	0.481	≥ 35	51.6	42.4	0.391	0.571	0.245
SII	0.622	≥ 757.96	60.4	54.2	0.545	0.699	*0.004**

* p< 0.05
ARUC: Area under curve, WBC: White blood cell count, NLR: Neutrophil to lymphocyte ratio, IGC: Immature granulocyte count, SII: Systemic immune-inflammation index, CI: Coefficient interval.

DISCUSSION

This study demonstrated that a high SII value and a high NLR may be possible predictors of the need for invasive treatment in patients with NSTEMI-ACS.

Distinguishing NSTEMI-ACS patients who need invasive treatment from others may be important in terms of decreasing cardiovascular mortality, under COVID-19 pandemic conditions. In the literature, there is a lack of literature about the roles of inflammatory hematological markers with predictive properties for cardiovascular mortality in these patients.

One of the main mechanisms that play a role in increasing the tendency of the atheroma plaque to rupture is inflammation[10,11]. Leukocytosis, neutrophilia and lymphopenia have been reported to indicate a poor prognosis in ACS[12-14]. NLR, a potential inflammation biomarker, is a marker that provides information about the complex inflammatory activity in the vascular bed in NSTEMI-ACS[14]. In recent years, it has been reported that the number of immature granulocytes may be used as a prognostic indicator, especially in malignancies[15]. It has also been shown to predict high syntax score in patients with ACS[16].

Platelet activation is one of the main mechanisms involved in the etiopathogenesis of ACS. It has been reported that a high platelet count and a decreased lymphocyte count may be associated with a potential thrombotic state and increased inflammation[17]. Thrombocytosis, PLR, MPV, and PDW has also been reported to be associated with adverse cardiovascular events[18,19]. However, none of these parameters had a significant correlation with the invasive treatment method.

Recently, it has been reported that increased levels of SII, which was developed to evaluate the inflammatory and immune status of patients simultaneously, are associated with poor prognosis in cancer disease[9,20,21]. Also, in coronary patients undergoing percutaneous coronary intervention, it was observed that the high SII value predicts major cardiovascular events better than traditional risk factors[7].

This study is probably the first to investigate hematological markers of inflammation in distinguishing patients with NSTEMI-ACS who need invasive therapy. It is vital to differentiate these patients during the COVID-19 pandemic period when invasive treatment strategies cannot be applied to all patients. In this study, it was seen that high WBC, NLR value and SII moderately predicted the need for an invasive treatment strategy in the initial evaluation of NSTEMI-ACS patients.

Its main limitations are that the design of the study is retrospective and the study volume is not large. Especially the relatively smaller number of patients, for whom medical treatment decisions were made, might be a limitation. Another limitation is that the biomarkers commonly used for atherosclerosis were not used in this study.

CONCLUSION

It is unclear whether the NLR and SII elevation, which may be a predictor of the need for invasive treatment, is a cause or a consequence of the pathophysiological process in patients with NSTEMI-ACS. However, elevated NLR and SII values can help distinguish NSTEMI-ACS patients who need invasive treatment during the COVID-19 pandemic. The results of this study, show the need for large-sized studies to determine the ideal cut-off point of NLR and SII levels in determining the treatment strategy for NSTEMI-ACS.

Ethics Committee Approval: The research protocol in line with the Helsinki Declaration was approved by the local ethics committee (Approval Date: 05.08.2020; Protocol No: 2020/15/10).

Informed Consent: Due to the design of the study, consent to volunteer could not be obtained from the patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - EA, MB; Analysis/Interpretation - EA, DA, MB; Data Collection - EA, EÇ, BÖ; Writing - EA; Critical Revision - EA, DA, KG, AA; Final Approval - EA, AA; Statistical Analysis - DA, MB; Overall Responsibility - EA.

Conflict of Interest: The authors have no conflicts of interest to declare

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Collet JP, Thiele H. The 'Ten Commandments' for the 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2020;41:3495-7. [Crossref]
2. Aktoz M, Altay H, Aslanger E, Atalar E, Atar I, Aytekin V, et al. Consensus Report from Turkish Society of Cardiology: COVID-19 and Cardiovascular Diseases. What cardiologists should know. (25th March 2020). Turk Kardiyol Dern Ars 2020;48:1-48. [Crossref]
3. Romaguera R, Cruz-Gonzales I, Ojeda S, Jimenez-Candil J, Calvo D, Seara JG, et al. Consensus document of the Interventional Cardiology and Heart Rhythm Associations of the Spanish Society of Cardiology on the management of invasive cardiac procedure rooms during the COVID-19 coronavirus outbreak. REC Interv Cardiol 2020;2:106-11. [Crossref]
4. Arbel Y, Finkelstein A, Halkin A, Birati EY, Revivo M, Zuzut M, et al. Neutrophil/lymphocyte ratio is related to the severity of coronary

artery disease and clinical outcome in patients undergoing angiography. Atherosclerosis 2012;225:456-60. [Crossref]

5. Yang YL, Wu CH, Hsu PF, Chen SC, Huang SS, Chan WL, et al. Systemic immune-inflammation index (SII) predicted clinical outcome in patients with coronary artery disease. Eur J Clin Invest 2020;50:e13230. [Crossref]
6. Tang EW, Wong CK, Herbison P. Global Registry of Acute Coronary Events (GRACE) hospital discharge risk score accurately predicts long-term mortality post acute coronary syndrome. Am Heart J 2007;153:29-35. [Crossref]
7. Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res 2014;20:6212-22. [Crossref]
8. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. Am J Cardiol 1983;51:606. [Crossref]
9. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-63. [Crossref]
10. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. N Engl J Med 2013;368:2004-13. [Crossref]
11. Madjid M, Fatemi O. Components of the complete blood count as risk predictors for coronary heart disease: in-depth review and update. Tex Heart Inst J 2013;40:17-29. [Crossref]
12. Bian C, Wu Y, Shi Y, Xu G, Wang J, Xiang M, et al. Predictive value of the relative lymphocyte count in coronary heart disease. Heart Vessels 2010;25:469-73. [Crossref]
13. Cannon CP, McCabe CH, Wilcox RG, Bentley JH, Braunwald E. Association of white blood cell count with increased mortality in acute myocardial infarction and unstable angina pectoris. OPUS-TIMI 16 Investigators. Am J Cardiol 2001;87:636-9. [Crossref]
14. Tamhane UU, Aneja S, Montgomery D, Rogers EK, Eagle KA, Gurm HS. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. Am J Cardiol 2008;102:653-7. [Crossref]
15. Bozan MB, Yazar FM, Kale İT, Yüzbaşıoğlu MF, Boran ÖF, Azak Bozan A. Delta neutrophil index and neutrophil-to-lymphocyte ratio in the differentiation of thyroid malignancy and nodular goiter. World J Surg 2021;45:507-14. [Crossref]
16. Bedel C, Korkut M, Aksoy F, Kuş G. Usefulness of immature granulocytes to predict high coronary SYNTAX score in acute coronary syndrome; a cross-sectional study. Arch Acad Emerg Med 2020;8:e73. [Crossref]
17. Azab B, Shah N, Akerman M, McGinn JT Jr. Value of platelet/lymphocyte ratio as a predictor of all-cause mortality after non-ST-elevation myocardial infarction. J Thromb Thrombolysis 2012;34:326-34. [Crossref]
18. Nikolsky E, Grines CL, Cox DA, Garcia E, Tcheng JE, Sadeghi M, et al. Impact of baseline platelet count in patients undergoing primary percutaneous coronary intervention in acute myocardial infarction (from the CADILLAC trial). Am J Cardiol 2007;99:1055-61. [Crossref]
19. Budzianowski J, Pieszko K, Burchardt P, Rzezniczak J, Hiczkiewicz J. The role of hematological indices in patients with acute coronary syndrome. Dis Markers 2017;2017:3041565. [Crossref]
20. Yang R, Chang Q, Meng X, Gao N, Wang W. Prognostic value of systemic immune-inflammation index in cancer: a meta-analysis. J Cancer 2018;9:3295-302. [Crossref]
21. Zhong JH, Huang DH, Chen ZY. Prognostic role of systemic immune-inflammation index in solid tumors: a systematic review and meta-analysis. Oncotarget 2017;8:75381-8. [Crossref]